The "chronic immune polyradiculopathies": diverse but maybe just CIDP after all

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In 2004, Sinnreich et al. reported 15 subjects with a pure sensory disorder of peripheral origin, with no electrophysiologic sensory correlate on conventional nerve conduction studies [1]. These patients presented with severe sensory ataxia and functional impairment. The site of the lesion was presumed to be proximal to the dorsal root ganglion and this was supported by abnormal sensory evoked potentials (SSEPs) and normal central nervous system MRI (magnetic resonance imaging) in all, as well as by MRI abnormalities affecting the dorsal sensory rootlets, in 5 of the 15 patients. Cerebrospinal fluid protein was elevated in 13. Neuropathologic studies of biopsied sensory rootlets showed inflammatory changes in 3. Importantly, treatment with corticosteroids or intravenous immunoglobulin proved effective in 6 in improving function, with 4 returning to normal ambulation. They coined the disorder "CISP", for "chronic immune sensory polyradiculopathy".

In the current issue of *Muscle & Nerve*, Khadilkar et al. report on 8 further patients with CISP, its postulated motor counterpart, and a mixed sensorimotor form [2]. They propose as a result, new terminology to describe the predominant system involved in these "chronic immune polyradiculopathies". Two of their patients had CISP, 2 had the motor variant and 4 had a sensorimotor form. Of interest, all patients displayed absent lower limb F-responses, except one, in whom they were impersistent. SSEPs were abnormal in all and CSF protein was raised in all. MRI, performed in all 8 subjects, demonstrated thickening and contrast

enhancement of the lumbosacral roots in all. Every patient responded to corticosteroids and immunosuppressants as assessed by the Modified Rankin scale.

Their series is of great interest in the setting of the increasing complexity of the chronic inflammatory demyelinating polyneuropathy (CIDP) spectrum, but at the same time also represents a useful opportunity to re-visit the specific entity which has been described as represented by these polyradiculopathies, although to date in only a small number of published reports. This is important because, on the one hand, splitting these from CIDP means those patients should be considered as harboring different disorders, implying, suddenly, that only anecdotal evidence would exist to support their treatment modalities, as opposed to the strong evidence available for CIDP. This obviously, in practice, would prove unhelpful for patients and their treating neurologists, especially in view of the increasingly regulated availability of immunoglobulins worldwide. On the other hand, lumping them with CIDP may be understandably debatable, as these patients do not display motor demyelination, and in CISP, any peripheral electrophysiological abnormality whatsoever.

There have been few published descriptions of “chronic immune polyradiculopathies” since Sinnreich’s initial paper. Experience from clinicians in centers with expertise in dysimmune neuropathies indicates these are very rare, but encountered, sometimes in what could be considered as somewhat even more atypical forms, with additional associated features [3-5]. The presence of sensory ataxia clinically, with areflexia and normal motor function, is for the neurologist, a red flag. This may or may not be supported by the above-mentioned tests, after overcoming the initial surprise of entirely normal conventional motor and especially, sensory electrophysiology. This infrequently encountered syndrome being potentially severely

disabling, but treatable, the question of using corticosteroids, and if contraindicated or ineffective, intravenous immunoglobulin or plasma exchanges, and in persistent refractory cases, even immunosuppression, is posed. Thus, CISP was classified as an atypical CIDP variant within the spectrum of CIDP in the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 Guidelines [6]. However, although clinically compatible with a sensory ataxic, and therefore atypical, CIDP, CISP does not meet electrophysiological requirements for the disorder. Furthermore, CSF protein elevation may be inconstant and recent data indicates the need for age-based cut-offs to define abnormal values, increasing uncertainty about its diagnostic value in the setting of additional suboptimal specificity [7]. Nerve MRI in the setting of immune-mediated neuropathy also poses problems of its own, especially given its recently confirmed low inter-rater reliability [8]. As regards SSEPs, their value is uncertain as specificity may be an issue, due to multiple other potential causes of undetectable responses and their lack of localizing value. Pathologic studies as described in the original paper are seldom possible in practice in most units as they require an invasive lumbar root biopsy with specialized peripheral nerve neuropathology. Hence, the diagnosis of CISP is not straightforward and reliance on the presence of clinical sensory ataxia with normal sensory conduction nerve conduction studies remains paramount.

A first case of a postulated pure motor variant of CISP, labelled “CIMP” for “chronic immune demyelinating motor polyradiculopathy” was described by O’Ferrall et al. in 2013 [9]. Their patient presented with back pain and progressive, pure motor weakness of the proximal and distal lower limbs over 10 years. Electrophysiology showed reduced fibular motor amplitudes with absent fibular and, of note, prolonged tibial F-responses. No other

conduction abnormality was present, including on sensory studies. EMG revealed multi-myotomal acute and chronic denervation in lower limb muscles. Genetic studies excluded a PMP22 duplication. MRI demonstrated a thickened and contrast-enhancing cauda equina and CSF protein was elevated. A fascicular nerve root biopsy was performed and revealed numerous onion bulbs and loss of myelinated fibers but no inflammatory infiltrates. The patient failed a trial of immunoglobulins and corticosteroids but responded to plasma exchanges.

The first sensorimotor description of "chronic immune polyradiculopathy" dates back to 2017, also by Dr. Khadilkar's group, who reported exclusively proximal lower limb weakness in one, proximal as well as distal lower limb weakness in the other, but upper limb sparing in both [10]. Reflexes were absent only in the legs. Proprioceptive involvement was marked in both patients, but again sparing the upper limbs. Electrophysiology showed normal sensory studies, with motor studies showing no abnormality, except absent/impersistent F-waves affecting lower limb nerves only. SSEPs showed absent lumbar root potentials and delayed or absent cortical potentials from tibial nerve stimulations. CSF protein was raised in both and MRI showed contrast enhancement and thickening of the lumbosacral roots in one patient. Both patients responded favorably to corticosteroids and immunosuppressants with significant improvements in Modified Rankin scores. They termed the disorder "chronic immune sensorimotor polyradiculopathy" ("CISMP"). A further 9 patients with postulated "CISMP" were described by Thammongkolchai et al. in 2019, with what the authors described as clinically "classic CIDP" but electrophysiological findings of pure polyradiculopathy for which structural, infectious or neoplastic processes had been excluded

[11]. All had weakness, but, importantly, proximal only in 4, and with, interestingly, exclusive cranial involvement in one. Sensory symptoms were present in all but ataxia was clearly present only in one. Lower limb areflexia was present in all and cranial nerve dysfunction in 3. Electrophysiology showed preserved sensory conduction studies. Motor amplitudes were on the whole, normal, with no evidence of demyelination. However, F-waves, performed in only one ulnar and one tibial nerve, notably showed likely demyelinating-range prolongation of latencies in 4/9, moderate prolongation in 2/9 and absence in 1/9. Multi-myotomal lower limb active and chronic denervation was present in all subjects. Further investigations showed elevated CSF protein in 8/9 and contrast enhancement of the lumbosacral nerve roots in 8/9, with 5/9 exhibiting root thickening. With corticosteroids, immunoglobulins and immunosuppressants, alone or in combination, all equally displayed improvement on the Modified Rankin scale.

One of the main issues with these “chronic immune polyradiculopathies” relates to the extent of distal nerve segment preservation from inflammatory demyelination. Of relevance, we reported a patient with a CISP phenotype, but who displayed some limited degree of post-ganglionic sensory electrophysiological involvement, while meeting all other criteria for CISP and responding remarkably to immunoglobulin treatment, after corticosteroid-induced deterioration [4]. Some spreading of the pathologic process beyond the dorsal root ganglion adds the word “neuropathy” to “chronic immune polyradiculopathy”, and if this involves motor fibres with slowed conductions, the word “demyelinating”, also comes into play, making it, potentially, simply, “CIDP”. The description of “chronic immune polyradiculopathy” appears hence purely anatomical, with an overreliance on the ability of

electrophysiology to precisely localize. CIDP is known to affect nerves in a patchy manner and heterogeneous clinical as well as electrophysiological presentations are as a result, unsurprisingly. A second important question is how far we go to demonstrate inflammatory demyelination electrophysiologically. Simply and intuitively, less extensive testing is less likely to achieve the diagnosis, as we previously showed [12]. It is otherwise equally unsurprising that distal motor latencies and motor conduction velocities are normal when the pathology is proximal, just as are the absence of conduction block and temporal dispersion. However, as described in Khadilkar et al.'s current series [2], F-wave abnormalities are indicative of motor root pathology even in absence of clinical weakness, in many of these patients. It is noteworthy that the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) Guidelines considers both F-wave prolongation and absence as part of the electrodiagnostic criteria for CIDP [6]. Several described subjects had such abnormalities, but the studies, as detailed, were of limited extensiveness, a known reason for electrophysiological underdiagnosis of CIDP [12, 13]. This, as a result, makes them inconclusive instead of allowing, as postulated, the exclusion of CIDP. In addition, it is known that pure inflammatory sensory neuropathic disease may present with asymptomatic proximal segment motor abnormalities, including conduction blocks [3], as we have also found in our experience [14]. These were not sought for in any of the above-mentioned reports. Regarding the stated MRI findings, as opposed to Sinnreich et al.'s initial paper which described exclusive sensory rootlet abnormalities, subsequent reports all demonstrate post-ganglionic segment changes, consistent with what is reported in CIDP, albeit with the limitations of the MRI technique.

What could one therefore conclude about the concept of the "chronic immune polyradiculopathies" for clinical practice? The published descriptions certainly add to knowledge in the field in relation to phenotype variability, but going back to the basics, the clinical presentation can be sensory, motor or sensorimotor, and thus, remarkably reminiscent of sensory, motor and sensorimotor CIDP. The frequent lower limb-exclusive presentation in the published series is reminiscent of the lumbosacral CIDP variant described by Caporale et al. [15], representing a focal form of the disorder, also already clearly within EFNS/PNS criteria of 2010, as a form of "atypical" CIDP [6]. In addition, several of the reported patients had other features such as exclusively distal weakness or cranial nerve involvement, again suggesting they form part of the established variants of "atypical" CIDP. The electrophysiology in the published reports, finally and importantly, clearly indicates insufficient testing, not only in the number of nerves studied and the stimulation sites (none had bilateral 8-nerve studies or proximal upper limb nerve stimulations up to Erb's point [12, 16]), but also in that of the considered parameters (distal compound muscle action potential durations, for example, although of substantial diagnostic value for CIDP [17, 18], were absent from all reports). Although unfortunately common in practice, this is evidently problematic here in justifying the concept of an entity separate from CIDP.

The CIDP field is evolving and the newly-described antiparanodal antibody positive cases well-illustrate this [19]. The pathology in such cases is neither inflammatory nor demyelinating, the treatment likely to be different, and this may suggest they should be considered separately [20]. As regards the "chronic immune polyradiculopathies" however, given the clinical picture, the available albeit limited pathologic data, the absence of certainty

of non-fulfilment of EFNS/PNS electrophysiological criteria, and the reported response to conventional treatments, such a need for separation is difficult to justify. The EFNS/PNS CIDP Guidelines and criteria require revision and this process, already under way, will hopefully be successful in helping and simplifying the diagnostic process of what is an increasingly heterogeneous disorder. Lumping rather than further splitting, on this occasion, requires careful consideration. On this may depend easing the diagnosis and access to treatment for affected patients, which, ultimately, is what really matters.

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